## REMARKS

At the outset, Applicants' thank the Examiner for graciously granting Applicants' representative a telephonic interview on September 2, 2005. During the interview, claim amendments were discussed which address the objections and rejections set forth in the Final Office Action. The substance of the interview is included in the remarks set forth below.

Claims 1, 2, 4, 5, 7-16 and 25-35 were pending in the application. By the present amendment, claims 1 and 5 have been cancelled, and claims 2, 4, 7, 9-12, 15-16, 24-27, 33 and 34 have been amended. Support for the amendments to the claims can be found throughout the specification as filed. *No new matter has been added.*

Accordingly, upon entry of the present amendment, claims 2, 4, 7-16 and 24-35 will be pending. Amendment and/or cancellation of the claims should in no way be construed as acquiescence to any of the rejections and was done solely to more particularly point out and distinctly claim the subject matter that Applicant believes to be his invention in order to expedite prosecution. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

### *Objections to the Claims*

Claim 7, 8 and 10 were objected to under 37 CFR § 1.75(c) as being in improper dependent form because multiple dependent claims cannot depend from any other multiple dependent claim. This objection has been rendered moot by the cancellation of claim 5 and the amendment of claim 7 to depend from independent claims 2 and 4.

The previous objection to claims 1, 5, 9, 15-16 and 24-35 was maintained on the ground that claim 1 is still unclear. This objection has been rendered moot by the cancellation of claim 1 and the amendment of the remaining claims to depend from independent claims 2 and/or 4.

The previous objection to claims 2, 5, 9, 15-16 and 24-35 was maintained on the ground that the use of the term "TDCPA" is still unclear. The claims have now been amended to specify the subject as categorized "as being likely to have prostate cancer using one or more diagnostic tests selected from the group consisting of rectal examination, transrectal ultrasonography, magnetic resonance imaging, bone scanning, X-ray, skeletal survey,

intravenous pyelography, CAT-scan, biopsy and an assay for the detection of a prostate cancer marker." Accordingly, withdrawal of this objection is respectfully requested.

The objection to claim 33 was maintained on the ground that "it is not clear what 'a percent-free prostate specific antigen of between about 15 and about 25%' is." This objection has been rendered moot by the amendment of claim 33, as suggested by the Examiner, to recite "a percent of free prostate specific antigen, as opposed to bound prostate specific antigen, of between about 15% and about 25%."

***Rejections Under 35 U.S.C. 112, First Paragraph***

The rejection of claims 1-2, 4-5, 7-16 and 24-35 as failing to comply with the enablement requirement was maintained on the ground that "the language "human Pin" in claims 1-2, 4-5, 7-16, 24-35, without being specified that the human Pin1 is SEQ ID NO:1 in the claims, encompasses variants of SEQ ID NO:1, with unknown structure..."

Applicants respectfully traverse this rejection. However, in the interest of expediting prosecution, and in no way acquiescing to the Examiner's rejection, the claims have been amended to be specify that the Pin1 in the biological sample is detected using a "*an antibody for a Pin1 polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1 or an antigen binding fragment thereof.*" Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

***Additional Issues***

During the interview held on September 2, 2005, the Examiner also requested that the claims be amended to specify that the biological sample comprises prostate cancer cells in order to add further clarity to the claimed subject matter. While Applicants' do not agree that such an amendment is necessary to clearly set forth the metes and bounds of the claimed inventions, they have agreed to amend the claims as suggested by the Examiner to expedite prosecution.

With regard to claim 32, the Examiner requested Applicants' to confirm that the expression of PSA velocity as *ng/ml per year*, as defined in the specification at page 28, lines 17-20, is the art-recognized form of expressing this measurement. As confirmatory evidence

that the expression of PSA velocity by ng/mL per year was widely recognized by the skilled artisan as of the filing date of the application, Applicants' submit herewith as Appendix A, a copy of an article published entitled "Prostate-Specific Antigen (PSA) Best Practice Policy. American Urological Association (AUA)," *Oncology* (Williston Park), 14(2):267-72, 277-8, 280 passim. (February 2000), http://www.cancernetwork.com/journals/oncology/o0002e.htm. In particular, Applicants' direct the Examiner's attention to the fourth to sixth sentences of the fourth full paragraph on page 4 of the copy provided which states,

> Another way to improve sensitivity is to follow serum PSA values in an individual patient over time (PSA velocity). If a rising trend in the PSA level is detected, a prostate biopsy may be considered. Some investigators have suggested that *a rise of 0.75 ng/mL or greater in a year* is a reason for concern. (emphasis added)

## SUMMARY

In view of the above amendment, applicant believes the pending application is in condition for allowance.

A petition for the appropriate extension of time is being filed concurrently herewith. However, if any additional fees are due, please charge our Deposit Account No. 12-0080, under Order No. PTZ-007 from which the undersigned is authorized to draw.

Dated: September 6, 2005

Respectfully submitted,

By _____

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From the American Urological Association

# Prostate-Specific Antigen (PSA) Best Practice Policy



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**Prostate cancer is the most common form of noncutaneous cancer in men in the United States. Despite its prevalence, the natural history of this disease is remarkably heterogeneous. In many patients, the cancer progresses slowly, resulting in moderately or poorly differentiated tumors that remain localized to the prostate gland. Although potentially life-threatening, such cancers are often curable. In other patients, however, tumor growth is rapid and can spread beyond the confines of the prostate. In such cases, the cancer is not curable, and long-term survival is considerably diminished. Strategies for managing prostate cancer have therefore been aimed at early detection and local treatment of the cancer. Prostate-specific antigen (PSA) is a tumor marker currently used for early detection of prostate cancer. Measurement of serum PSA levels has significant clinical application in other areas of prostate disease management. The purpose of this report is to provide current information on the use of PSA testing for: (1) the evaluation of men at risk for prostate cancer, (2) assistance in pretreatment staging, and (3) the posttreatment monitoring and management of men with this disease. The following summary is based on a review of the literature and the expert opinions of a multispecialty panel convened by the American Urological Association (AUA). It is intended to serve as a resource for urologists and primary care physicians. [ONCOLOGY 14(2):267-286, 2000]**

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## Introduction

Prostate-specific antigen (PSA) is a glycoprotein produced primarily by the epithelial cells that line the acini and ducts of the prostate gland. PSA is concentrated in prostatic tissue, and serum PSA levels are normally very low. Disruption of the normal prostatic architecture, such as by prostatic disease, allows greater amounts of PSA to enter the general circulation. Elevated serum PSA levels have become an important marker of prostate pathologies—which include benign prostatic hyperplasia, prostatitis, and especially prostate cancer, the focus of this document. Prostatic intraepithelial neoplasia (PIN) does not appear to raise serum PSA levels.[1]

## The Use of PSA for Early Detection of Prostate Cancer

Prostate cancer is the most common form of noncutaneous cancer in men in the United States, and the second leading cause of male cancer mortality, accounting for more than 30,000 deaths in 1999 (American Cancer Society). The natural history of this disease is remarkably heterogeneous and, at this time, is not clearly understood. Autopsy

studies have shown that approximately one in three men over the age of 50 years has histologic evidence of prostate cancer, with up to 80% of these tumors being microscopic in size or clinically insignificant. Fortunately, only about 3% of men will die from this disease.[2-4]

Some studies have found that a large proportion of patients diagnosed with clinically localized prostate cancer who did not receive early aggressive treatment still had favorable clinical outcomes and normal life expectancies.[4] Most of these studies included an older population of men as well as a larger proportion of men with low-grade tumors than in a series of men treated for prostate cancer. This disparity between the high prevalence rates for histologic prostate cancer and the relatively low lifetime risk of prostate cancer death highlights the difficulty in distinguishing cancers destined to cause significant illness and premature death from those that will not.

PSA testing is one of several measures that can be used to identify high-risk tumors (Figure 1). Other such measures include: Gleason score, clinical stage, and the patient's estimated life expectancy.[5,6] Because of the biological variability of prostate cancer and the lack of a completed randomized, controlled trial that proves the benefit of early detection, the use of PSA for prostate cancer early detection remains controversial.[7]

**1. The goal of early prostate cancer detection.**

The goal of early detection is to identify patients who have clinically significant prostate cancers, ie, cancers that are at an early stage when treatment is most likely to be effective. The risk of prostate cancer death can be substantial, especially in younger patients with moderate- or high-grade tumors. Studies have shown that long-term survival is considerably diminished in men diagnosed with prostate cancer that has already spread beyond the confines of the prostate to regional lymph nodes or more distant sites. In general, tumors in such cases are not curable, although patients may benefit from palliative therapies.[5] "Cure" is defined in this document as lifetime freedom from the disease.

**2. The proportion of clinically significant prostate cancer detected with PSA is unknown.**

There is currently no universally accepted definition of what is clinically significant or insignificant prostate cancer. Ideally, such a determination would be made using only information obtained noninvasively, allowing an accurate decision to avoid aggressive therapy in certain patients. Previous studies have focused on measures such as cancer volume, pathologic stage, surgical margin status, and biopsy histologic grade.[8-12]

Tumor grade appears to be the strongest prognostic factor, although such assessments, even from multiple biopsy specimens, are subject to sampling errors.[8,9] The most common system currently in use is the Gleason grading system based on architectural criteria.[13] The pathologist assigns a primary grade from 1 to 5, with 5 being the most aggressive, to the pattern occupying the greatest area of the specimen. A secondary grade is then assigned to the pattern occupying the second largest area. These two grades are added to determine the Gleason score, which ranges from 2 to 10. It is generally agreed that tumors with a Gleason score of 2 to 4 have lower biological aggressiveness, scores of 5 to 6 have an intermediate aggressiveness, and those with a Gleason score $\geq 7$ are biologically aggressive tumors.[14]

Tumor volume exceeding 0.5 mL (a characteristic of roughly one-fifth of prostate cancers discovered during incidental autopsies) is considered by many experts to predict clinical significance. Tumors that exceed 0.5 to 1.9 mL of volume appear to produce sufficient amounts of serum PSA to exceed the normal range and begin to exhibit spread beyond the prostate (extraprostatic disease).[15-17] No currently available noninvasive imaging method(s) can reliably measure tumor volume.[18]

Several studies have found that a very large proportion of cancers detected through PSA testing are likely to be clinically important, but that PSA testing is unlikely to detect many of the more prevalent small-volume histologic

cancers.[7,19,20] Only a small proportion of prostate tumors detected by PSA and treated with radical prostatectomy are subsequently found to be clinically insignificant (ie, very small and low grade).[9,19-22]

Approximately one-third of cancers found through early detection efforts with PSA and treated surgically have evidence of extracapsular spread, poorly differentiated histology, large tumor volume, or distant metastasis.[9,19-21] Although these features do not always indicate a poor outcome or ultimate death from the disease, they correlate with a significantly greater chance of disease progression. Also of note, autopsy studies have found capsular penetration, lymph node spread, and poorly differentiated tumors in a limited number of patients with no clinical suspicion of prostate cancer.[4]

Recent data suggest that combinations of preoperative data, including PSA level, clinical stage, and Gleason score from biopsy, can significantly enhance the ability to predict actual pathologic stage.[23] The value of such combinations, however, for clinical decision-making with individual patients remains uncertain.

**3. PSA testing detects more tumors than does DRE, and it detects them earlier. However, the most sensitive method for early detection of prostate cancer uses both DRE and PSA. Both tests should be employed in a program of early prostate cancer detection.**

Prior to the use of PSA for early detection of prostate cancer, digital rectal examination (DRE) detected considerably fewer tumors. It is generally accepted that the dramatic increase (by 82% in men over age 65 years) in prostate cancer detection between 1986 and 1991 was due to the proliferation of PSA testing.[24,25] Of prostate cancers currently detected, about 75% have an abnormal PSA.

During the pre-PSA era (before about 1986-1987), as many as 35% of all patients with what was thought to be clinically confined prostate cancer were found to have positive lymph nodes, and two-thirds had pathologically advanced disease.[26,27] Currently, lymph node involvement is noted in less than 5% of patients, and there is evidence that serial PSA testing (eg, yearly testing) has led to a decrease in the number of patients with pathologically advanced disease.[23,28]

PSA testing thus detects more tumors than does DRE and detects them earlier. Although many of these tumors have aggressive characteristics, some may grow slowly enough that they pose no risk to the patient. As yet, there is no way to identify with certainty the tumor that has no risk of spreading and potentially causing premature death or morbidity.[21,29]

PSA is currently the best single test for early prostate cancer detection, but the combination of PSA and DRE is better—because DRE will detect some of the tumors in patients who have prostate cancer despite a normal PSA of less than 4.0 ng/mL.[4,30] Transrectal ultrasonography is not a useful test for early prostate cancer detection; it adds little to the combination of PSA and DRE.[4,30]

Evidence from three uncontrolled studies that allow a direct comparison of the yields of PSA and DRE suggests that combining both tests improves the overall rate of prostate cancer detection when compared with either test alone.[31-33] In these studies, volunteers were tested uniformly with both PSA and DRE. From 18% to 26% of patients had either an abnormal PSA or an abnormal DRE. Cancer was detected in 3.5% to 4.0% of patients. Although PSA identified a larger number of cancers than did DRE, PSA and DRE each detected cancers not identified by the other. Also of note, approximately 20% of prostate cancers with aggressive features are found in men whose PSA level is less than 4 ng/mL.[31]

There is clearly strong evidence in favor of including both DRE and PSA in any program for early detection of prostate cancer. However, the value of serial determinations of PSA or DRE in patients with a normal initial examination is unknown.[4] There is evidence, as mentioned previously, that serial PSA determinations lead to a

decrease in detection of pathologically advanced disease.[28]

**4. A variety of factors can affect PSA and should be considered in the interpretation of results.**

The three most common prostatic diseases—prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer—can all be associated with elevations of serum PSA levels. Other factors that are known to cause secondary elevations in PSA levels include: physical activity, infection, and/or medications. Medications can also suppress PSA levels, resulting in false-negatives on tests. It is therefore important to take a careful medical history prior to assessing the PSA value in a patient.[34,35] Surgical castration or medical castration (with LHRH-agonist or antiandrogen therapy) will lower PSA, often dramatically. Finasteride, a 5-alpha reductase inhibitor used for the treatment of BPH and male pattern baldness, will lower PSA by an average of 50%.[34]

Various herbal medicines may affect PSA as well. Saw palmetto (Serenoa repens), frequently taken for "prostate conditions," has been suggested to inhibit 5-alpha reductase, but in one large randomized trial, no impact on PSA was noted.[35] The herbal compound PC SPES has been found to lower PSA in a small series of patients. Because many men are currently using herbal supplements, it is important to obtain a careful medical history prior to assessing the PSA value in an individual patient.

Ejaculation and DRE have been reported to increase PSA levels, but studies have shown the effects to be variable or insignificant.[36] For this reason, PSA testing can be performed with reasonable accuracy after rectal examination.[37] Prostate biopsy and cystoscopy, however, will usually cause substantial elevation of PSA, and PSA testing should be postponed for at least 3 to 4 weeks due to this effect.[37]

**5. Sensitivity and specificity issues relating to the performance of PSA: Although methods exist to improve cancer detection rates or to decrease the number of unnecessary prostate biopsies, each method involves a tradeoff and should be discussed with the patient.**

From the standpoint of a patient undergoing PSA testing for prostate cancer, two major questions he might have are:

1. "What is the likelihood that, if I do have prostate cancer, the test will detect it?"

2. "What is the likelihood that, if I don't have prostate cancer, the test will suggest that I do?"

PSA testing in patients with normal serum PSA levels (defined as 4.0 ng/mL or less) has a sensitivity of about 67.5% to 80%.[38,39] In other words, approximately 20% to 30% of tumors will be missed when PSA is used alone. One way to improve sensitivity is to adjust the "normal" PSA level to a lower value for younger men (age-adjusted PSA). Men in their 40s, for example, should have a serum PSA of 2.5 ng/mL or less.[40] Another way to improve sensitivity is to follow serum PSA values in an individual patient over time (PSA velocity). If a rising trend in the PSA level is detected, a prostate biopsy may be considered. Some investigators have suggested that a rise of 0.75 ng/mL or greater in a year is reason for concern.[41] Both age-adjusted PSA and PSA velocity will increase the number of cancers detected, but both will also increase the number of men undergoing biopsy.

The specificity of PSA testing is 60% to 70% when the PSA level is > 4.0 ng/mL.[39] Several methods have been suggested to increase PSA specificity for prostate cancer and thus reduce the number of unnecessary biopsies. (Only about one prostate biopsy in four currently finds prostate cancer.[42]) One method to improve PSA specificity is age adjustment. Age adjustment consists of using higher "normal" PSA levels for older men. Because serum PSA tends to increase with age, the use of higher "normal" levels for older men results in fewer biopsies.[43] Table 1 shows several published "normal" age ranges for PSA, based upon the ethnic background of the patient.

Another method of improving PSA specificity, use of free-to-total PSA ratios, takes advantage of the fact that PSA

exists in the blood in two fractions—one bound to plasma proteins and the other in a free state. For reasons that are unclear, patients with prostate cancer tend to have lower free-total ratios, whereas men with benign disease have higher free-total ratios. Using the ratio of free-total PSA will reduce the number of biopsies in men with serum PSA levels between 4.0 and 10.0 ng/mL.[44,45] The optimal cut-off point for free-total PSA below which a prostate biopsy would be recommended, is unknown. Several authors have recommended the use of ratios ranging from 14% to 28%.[46]

There is a third method of improving PSA specificity. Because larger prostates produce larger amounts of PSA, adjusting the normal value for the size of the prostate (PSA density = PSA/gland volume) reduces the number of biopsies performed.[47]

All three methods—age-adjusted PSA, free-to-total PSA ratio, PSA density—will reduce the number of biopsies in men who do not have prostate cancer. The tradeoff is that all three also increase the risk that some prostate cancers will be missed.

Because of potential tradeoffs between sensitivity and specificity, there is at present no consensus on optimal strategies for using the different modifications of PSA testing. Clearly, however, adjusting the way PSA is used to determine the need for a prostate biopsy should be done for a purpose—either to increase prostate cancer detection or to reduce the risk of an unnecessary biopsy.

**6. When is a prostate biopsy indicated?**

Although an abnormal DRE or an elevated PSA may suggest the presence of prostate cancer, cancer can only be confirmed by the pathologic examination of prostate tissue. A urologist should be consulted for a prostate biopsy when any of the following findings are present:

1. PSA is 4.0 ng/mL or more;
2. A significant PSA rise from one test to the next; or
3. DRE is abnormal.

Prostate tissue can be obtained in several ways. The most common method is by means of a transrectal, ultrasound-guided prostate biopsy, which is usually performed as an outpatient procedure without anesthesia. Such biopsies are rarely complicated by rectal bleeding, hematuria, or prostatic infection. After biopsy, blood in the stool or urine usually disappears after a few days. Blood in the semen can be seen for up to several weeks after biopsy.

It is important to note that ultrasonography alone cannot exclude the presence of prostate cancer. If a biopsy is indicated based on an abnormal DRE and/or PSA level, the biopsy should be performed irrespective of a "normal" transrectal ultrasound examination.

Occasionally, prostate cancer may be detected when tissue is removed from the central portion of the prostate, usually during surgery for prostatic enlargement (BPH). Tissue may be removed transurethrally during transurethral resection of the prostate (TURP) or through an open transabdominal approach for larger prostate glands. In these cases, prostate cancer is generally an incidental finding as it is usually unsuspected prior to surgery. Of note, there are no data to support the idea that a TURP lowers the risk of developing prostate cancer.

**7. Serum PSA is proportional to the risk and extent of prostate cancer.**

In addition to the two previously stated questions (section 5) that might be asked by a man undergoing PSA testing

for prostate cancer, there is a third even more basic question: "What is the likelihood that I have prostate cancer if I have an elevated (abnormal) PSA?" The answer largely depends on the level of serum PSA elevation.

The average man older than age 50 years has about a 20% to 30% likelihood of having prostate cancer if his serum PSA is above 4.0 ng/mL. However, if the patient with a PSA between 2.5 and 4.0 ng/mL undergoes a prostate biopsy, the likelihood of detection of prostate cancer is approximately 27%.[48] For levels above 10 ng/mL, the likelihood increases to between 42% to 64%.[4,7,31-33,49,50]

Elevations in PSA between 4.0 and 10.0 ng/mL, as compared with PSA levels of less than 4.0 ng/mL, increase the odds of clinically significant, intracapsular prostate cancer by 1.5- to 3-fold and the odds of extracapsular disease (outside the prostate) by 3- to 5-fold.[4,49] Partin and colleagues analyzed clinical and pathologic data in 4,133 men treated with radical prostatectomy for clinically localized prostate cancer.[23] Half of all prostate cancers with preoperative PSA levels of 4.0 to 10.0 ng/mL were found to be extraprostatic.

Levels of PSA greater than 10.0 ng/mL substantially increase the risk that a prostate cancer is extraprostatic.[4] In the Partin study, more than 80% of men whose preoperative serum PSA exceeded 20.0 ng/mL had cancers that were not organ-confined. Approximately 5% of men with PSA levels of 4.0-10.0 ng/mL had either seminal vesicle or lymph node involvement—increasing to approximately 15% for men whose PSA was between 20.0 and 30.0 ng/mL. The authors of this study found that integrating clinical stage and histologic tumor grade further refines the ability to predict whether a given PSA reflects pathologically confined disease.

Of note, among 943 subjects with a PSA of less than 4.0 ng/mL, although only 1% had lymph node involvement and 3% had seminal vesicle involvement, 32% had evidence of capsular penetration and thus were at greater risk of disease recurrence following treatment. Such data may be helpful when counseling men with newly diagnosed prostate cancer. Conversely, patients should also be aware that even a normal DRE together with a PSA of less than 4.0 ng/mL does not guarantee the absence of prostate cancer.[38]

**8. The decision to use PSA for the early detection of prostate cancer should be individualized. Patients should be informed of the known risks and the potential benefits.**

The incidence of prostate cancer mortality has recently been declining in the United States. Analyses of this and other recent trends in prostate cancer rates suggest that a number of factors may be responsible, one of which may be the proliferation of PSA screening for the purpose of early detection.[51] However, since no large, randomized, controlled trials evaluating the role of prostate cancer screening have been completed, it is not possible to state with certainty whether early detection and treatment of prostate cancer reduce the mortality rate.[52-55] Two trials are currently examining this question, one in Europe and one in the United States. Schroder and colleagues, in the European Randomized Study of Screening for Prostate Cancer, based in the Netherlands, are enrolling 190,000 men between 55 and 70 years of age in five European regions and expect completion by 2008.[56] In the United States, the National Cancer Institute, in the Prostate, Lung, and Colorectal and Ovarian Cancer Screening Trial, is enrolling 74,000 men ages 55 to 74 years with results expected in 2006.[57,58]

Until these randomized, controlled trials are completed, it will not be known whether the value (possible reduction in morbidity and mortality) of the early diagnosis of prostate cancer is sufficient to outweigh the cost and morbidity (for example, erectile dysfunction, incontinence, and anxiety) associated with disease treatment.[59-66 ]

Advanced prostate cancer is associated with significant morbidity. Bone pain, inanition, anemia, sexual dysfunction, ureteral obstruction, and bony fractures have all been associated with this disease. In addition, some treatments that are used to slow the disease or ameliorate its complications can cause toxicities. Active treatment, such as surgery (radical prostatectomy) and radiotherapy (external-beam radiation or brachytherapy with radioactive seeds), for localized prostate cancer also carry a risk of complications.

Potential complications of radical prostatectomy include surgical risks as well as the risk of incontinence and erectile dysfunction. Multiple studies have evaluated sexual function after prostatectomy, but because of inconsistencies in patient selection and inconsistent preoperative assessment of erectile function, interpretation is difficult and varied. Rates of postoperative erectile dysfunction in published series range from 29% to more than 80% of patients.[67-70] The degree of postoperative incontinence varies in published studies from mild to severe. Rates range from zero to more than 30% of patients.[68,69]

Radiotherapy, although without surgical risks, is associated with erectile dysfunction and bowel or bladder symptoms. Chronic irritative voiding symptoms develop in up to 5% of patients.[49,66,69,71-73] Rectal irritation occurs in up to 10% of patients, and decreased erectile function in up to 50% of patients.[49,66,69,71-73] These same complications have been associated with brachytherapy, but estimates of incidence are, as yet, preliminary and await analysis of multicenter experience with meaningful follow-up.

Decisions regarding early detection of prostate cancer should be individualized, and benefits and consequences should be discussed with the patient before PSA testing occurs. Not all men over age 50 years are appropriate candidates for screening efforts for this disease. Ideally, physicians should consider a number of factors, including patient age and comorbidity as well as preferences for the relevant potential outcomes. Some organizations have even recommended that informed consent should be obtained prior to PSA testing.[49]

**9. Early detection of prostate cancer should be offered to asymptomatic men 50 years of age or older with an estimated life expectancy of more than 10 years. It is reasonable to offer testing at an earlier age to men with defined risk factors, including men with a first-degree relative who has prostate cancer and African-American men.**

If early detection is offered, for most men it should begin at age 50 years, as disease prevalence prior to this age is low, and few studies exist in men under age 50 years.[74-82] Because of the relatively long natural history of most prostate cancers, early detection may not be beneficial to men with a limited life expectancy. A physician should assess the individual patient's health status to determine the appropriateness of PSA measurement at any given age (Table 2). For a review on estimating treatment benefits for the elderly, see Welch et al, 1996.[83]

No definitive cause for prostate cancer has been established, but epidemiologic and screening studies have suggested a number of etiologies and factors that may be taken into account in determining the appropriateness of PSA measurement. A higher incidence of prostate cancer is found, for example, among men with first-degree relatives who have the disease.[81,84-89] In addition, wide variations have been noted among ethnic groups, with African-American men at a substantially greater risk for developing the disease and at an earlier age than other ethnic groups.[81,86,90,93] Consideration should therefore be given to testing men at higher lifetime risk of this cancer, such as those with a family history of the disease and African-American men, at an earlier age.[81,84-93]

## The Use of PSA for Pretreatment Staging of Prostate Cancer

Routine radiologic staging, such as with bone scan, computed tomography (CT), or magnetic resonance imaging (MRI), or surgical staging with pelvic lymph node dissection (Figure 2) is not necessary in all cases of newly diagnosed prostate cancer.[94,95] Clinical examination can identify patients for whom such staging studies are appropriate.

**1. Pretreatment serum PSA predicts the response of prostate cancer to local therapy.**

Pretreatment serum PSA is an independent predictor of response to all forms of therapy.[94] Serum PSA levels correlate with the risk of extra-capsular extension, seminal vesicle invasion, and both regional and distant disease. Patients with serum PSA levels of less than 10.0 ng/mL are most likely to respond to local therapy.

**2. Routine use of a bone scan is not required for staging asymptomatic men with clinically localized prostate cancer when their PSA is equal to or less than 20.0 ng/mL.**

Of 852 patients from a Mayo Clinic review of newly diagnosed prostate cancer, 66% had a PSA concentration of ≤ 10.0 ng/mL and only 3 (0.8%) had a positive bone scan. Only 0.6% of men with a PSA between 10.1 and 15.0 ng/mL and 2.6% of men with a PSA between 15.1 and 20.0 ng/mL had a positive scan consistent with metastasis.[94] These findings have been replicated in several series.[95-97]

Bone scans are generally not necessary in patients with newly diagnosed prostate cancer who have a PSA less than 20.0 ng/mL unless the history or clinical examination suggests bony involvement. As metastatic disease is significantly more common in advanced local disease or in high-grade disease, and as some high-grade prostate cancers are PSA-negative, it is reasonable to consider bone scans at the time of diagnosis when the patient has poorly differentiated or high-grade, stage ≥ T3 prostate cancer, even if the PSA is < 10.0 ng/mL.[98]

**3. CT or MRI scans are generally not indicated for the staging of men with clinically localized prostate cancer when the PSA is less than 25.0 ng/mL.**

A CT scan is not a useful staging procedure for the vast majority of patients with newly diagnosed prostate cancer for whom the current incidence of positive lymph nodes is < 5%.[99,100] It is rarely positive when the PSA is less than 25.0 ng/mL. In one study of 173 men, no patient with a PSA less than 25.0 ng/mL had a positive scan. CT scan identification of pelvic adenopathy depends upon lymph node enlargement, and the correlation between nodal size and metastatic involvement is poor.[101] Although the histologic incidence of positive pelvic lymph nodes is substantial when PSA levels exceed 25.0 ng/mL, the sensitivity of CT scanning for detecting positive nodes is only about 30% to 35% even at these levels.[99]

MRI scanning using a body coil is also not a useful staging procedure in the vast majority of patients with newly diagnosed prostate cancer.[102] Its sensitivity for detecting nodal metastases, obtained from the analysis of seven studies using MRI, was only 34.8%.[100] The utility of endorectal coil MRI and magnetic resonance spectroscopy (MRS) for characterization of cancer stage and volume has not as yet been determined.[103,104]

The Prostascint scan uses radioisotope labeled antibodies to detect and locate prostate carcinoma. This scan has limited value for pretreatment staging. It has been used mainly to identify metastatic disease in patients who exhibit a rising PSA after radical prostatectomy.[105,106]

**4. Pelvic lymph node dissection for clinically localized prostate cancer may not be necessary if the PSA is less than 10.0 ng/mL or if the PSA is less than 20.0 ng/mL and the Gleason score is less than or equal to 6.0.**

Although pelvic lymph node dissection is often routinely performed in conjunction with radical retropubic prostatectomy, its morbidity must be considered, especially in cases where it offers little additional information.

Pretreatment PSA, supplemented with clinical stage and Gleason score information, can identify a subset of patients in whom the incidence of nodal metastases is very low (3% to 5%). Patients with a pretreatment PSA of less than 10.0 ng/mL rarely have nodal metastases. Similarly, a Gleason score ≤ 6 with a pretreatment PSA < 20.0 ng/mL is rarely associated with nodal metastases. These observations have been made in several large series of patients.[23,107-110]

## The Use of PSA in the Posttreatment Management of Prostate Cancer

**1. Periodic PSA determinations should be offered to detect disease recurrence.**

The early biochemical (PSA) detection of recurrence after definitive local therapy (Figure 3) may prompt further

treatment. The optimal strategy, including time of initiation, for such adjunctive therapy remains uncertain and it is the focus of ongoing clinical trials. Treatment options for recurrence following radical prostatectomy include salvage radiation therapy and androgen deprivation. Treatment options for recurrence after radiation therapy include androgen deprivation, cryotherapy and, in selected patients, salvage radical prostatectomy. Salvage therapies in both instances may be more effective if initiated early, but the overall impact of any form of salvage therapy is currently unknown. [111]

**2. Serum PSA should decrease and remain at undetectable levels after radical prostatectomy.**

A detectable PSA following radical prostatectomy is associated with eventual disease recurrence in most patients. [112,113] The median interval from PSA recurrence to cancer death is between 5 and 12 years, depending upon the cancer's Gleason score.

**3. Serum PSA should fall to a low level following radiation therapy and cryotherapy and should not rise on successive occasions.**

What constitutes an acceptable serum PSA after radiotherapy and cryotherapy is a matter of debate. After radiation, PSA declines slowly and the lowest value (nadir) is not reached for a median of 17 months. Investigators have generally chosen one of two methods to define biochemical absence of disease. The first method is the assessment of nadir PSA following treatment. Although there is no consensus target nadir value, it appears that patients who achieve very low (eg, < 0.5 ng/mL) or undetectable levels are not likely to demonstrate clinical or biochemical relapse following treatment, at least not within 5 years of treatment.[114-118] Similar findings have been reported for men undergoing cryotherapy.[119,120]

The second method, which is recommended by the American Society for Therapeutic Radiology and Oncology (ASTRO), defines biochemical recurrence on the basis of three consecutive rises in serum PSA above nadir. This group recommends that PSA be measured no more often than every 3 to 6 months to detect meaningful rises beyond the intrinsic variability of the assay.[121,122]

**4. The pattern of PSA rise after local therapy for prostate cancer can help distinguish between local and distant recurrence.**

When biochemical failure does occur following local therapy, the patterns of PSA elevation (time to elevation and doubling time), when analyzed along with the primary cancer grade and stage, predict the likelihood of local recurrence or distant relapse and may have therapeutic implications.[112,113,123]

Those patients whose serum PSA (1) fails to fall to undetectable levels after surgery or rises despite radiation or cryotherapy, (2) rises within 12 months of all forms of local treatment, or (3) doubles in less than 6 months are more likely to have distant disease. Patients who develop biochemical recurrence late (ie, > 24 months after local treatment) and who have PSA doubling times exceeding 12 months are more likely to develop persistent/recurrent local disease. [112,113,123-125]

**5. The nadir serum PSA and percent PSA decline at 3 and 6 months predict progression-free survival in men with metastatic prostate cancer treated with androgen deprivation. The degree of PSA decline following second-line treatment of metastatic disease correlates with disease survival.**

Serum PSA levels in patients with metastatic prostate cancer who receive androgen deprivation should decline. Both nadir PSA and the percent decline at 3 and 6 months predict progression-free survival. Patients whose serum PSA level becomes undetectable and those whose PSA decreases by 90% or more at 3 and 6 months are more likely to experience a prolonged progression-free survival.[126-128]

Most investigators accept a fall in serum PSA as an acceptable end point for the evaluation of response in those patients with hormone-refractory prostate cancer who undergo secondary treatment. A decrease in serum PSA level of 50% or greater at 8 weeks after beginning secondary therapy appears to be associated with improved survival, compared to either no changes or lesser changes in PSA level.[128]

**6. Bone scans are indicated for the detection of metastases following initial treatment for localized disease. The level of PSA that should prompt a bone scan is uncertain.**

Although some reports have suggested that the levels of PSA that indicate metastatic disease are lower in patients who have previously received treatment for their disease, early biochemical failure after local therapy is rarely associated with a positive bone scan. In the absence of bony or systemic symptoms, the probability of a positive bone scan was less than 5% until total

PSA increased to between 40.0 and 45.0 ng/mL. Gleason score, pathologic stage, preoperative PSA, and time to recurrence added no utility in predicting bone scan results.[129,130]

## Methods Used in Best Practice Policy Development

The AUA convened a multidisciplinary panel for the purpose of developing a resource about PSA testing for urologists and primary care physicians. Panel membership included a family physician, two internists, and a radiation oncologist as well as four urologists. Funding in support of panel activities was provided by the AUA. Panel members received no remuneration for their efforts, and each member provided a conflict of interest document.

The panel formulated its policy statements and recommendations by consensus, based on review of the literature and the panel members' own expert opinions. After panel members agreed on the general areas to be covered, each member took on the task of conceptualizing and writing a section of the document in an area where he had specific expertise. The panel later met to merge the individual manuscripts into a single document. Both before and after this merger, every part of the document was thoroughly critiqued by panel members in written comments and verbally in a series of conference calls. Over the course of successive manuscript revisions, the panel scrutinized and modified the conceptual framework, reworked the wording of key statements, and reexamined supporting evidence reported in the literature—until panel members reached consensus.

The panel did not use any particular methodology to develop its consensus statements. As noted above, these statements are based upon panel members' expert opinions and knowledge of the published literature, and are referenced with what the panel considered to be the most appropriate publications. The panel also did not address issues of costs or cost-effectiveness in this document or systematically incorporate patient values and preferences in the analysis. However, the panel did include in the document ample information to assist patients in decision-making regarding the early diagnosis, staging, and treatment follow-up of prostate cancer.

After the panel reached an initial consensus, 47 peer reviewers representing the following medical specialties reviewed the manuscript: family practice, internal medicine, radiology, oncology and urology. The panel made numerous document changes based on the insight from peer reviewers.

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